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(54) Title: BIODEGRADABLE POLYMER IMPLANT MATERIALS

(57) Abstract

A polymer implant material primarily for use as a biodegradable barrier film for the prevention of post-surgical adhesions comprises a substantially continuous polymeric film, which is biodegradable in vivo; has at least one surface which is non-adherent to protein, has a glass transition temperature not greater than 40 °C; has drape properties such that at human body temperature it could be wrapped round a one centimetre diameter rod without exhibiting spring back tendency; and has a tear strength such as to allow it to be sutured into position on or around an organ of the human body. The film of the invention is preferably a film polyester polyurethane, of which the polyester portion is preferably an aliphatic polyester, and which one surface at least has been made non-adherent to protein by means of a polysiloxane which is incorporated into the polymer by copolymerization or is mixed into the polymer or is present as a coating on the polymer.

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# BIODEGRADABLE POLYMER IMPLANT MATERIALS

This invention relates to biodegradable polymer materials useful as surgical implants and more particularly useful as barrier films for the prevention of post-surgical adhesions.

Adhesion formation is a frequent sequel to many surgical procedures and plays a major role in compromising results and causing complications. Adhesions are caused when abnormal tissue bonds to the surfaces of internal organs which have been traumatized or damaged during surgery. Such adhesions may abnormally join organs or other body tissues that should normally be separate. This may give rise to the need for revision surgery following, for example, graft, immplant and transplant surgery, with consequent cost and danger or discomfort to the patient.

Attempts have been made to prevent or minimise adhesion formation by introducing blocking materials or barrier films, for example, around flexure tendons. Materials such as metals, polymers and natural materials have been tried for this purpose. A woven material based on regenerated cellulose is currently marketed for this purpose by Johnson & Johnson under the registered trade mark "Interceed". Polymeric materials that have been tried for the purpose include nylon, cellophane, PTFE, polyethylene, siloxance elastomers and polylactic acid copolymer films. Some of these materials are not bidegradable and would therefore remain indefinitely in the body with unpredictable consequences. Those materials that are biodegradable are not wholly satisfactory for other reasons and it is thought that the use of barrier films for preventing adhesion formation is nowhere practised routinely by surgeons.

This invention provides a polymer film that is more effective than prior used blocking agents in the prevention of post-surgical adhesion formation and which has the further advantages of

(a) being biodegradable in vivo so as to be self-eliminating once it has accomplished its purpose, and (b) allowing some control of the the period of time over which biodegradation occurs.

According to the invention a substantially continuous polymeric film is provided for the prevention or reduction of post-surgical adhesion formation which film:

(a) is biodegradable (resorbable) in vivo;

(b) has at least one surface which is non-adherent (as herein defined) to protein;

(c) has a glass transition temperature below normal human body temperature;

(d) has drape properties such that at human body temperature it can be wrapped around a 1cm radius, preferably a 1 cm diameter, rod without exhibiting spring-back tendency; and

(e) has a tear strength such as to allow it to be sutured into position.

The expression "non-adherent to protein" in the context of this specification means that when tested by the "gelatin adhesion test" (Andrews et al, Clinical Materials, 1 (1986), page 9) with the gelatin solution being dried at 37°C for 48 hours, the polymer film exhibits a peeling energy for a 180° peel of less than 20J/m² at ambient temperature.

Preferably the polymer film exhibits a peeling energy of less than 10J/m² and more preferably less than 2 J/m² when tested by the above test.

In order to achieve non-adherence to protein for many types of biodegradable polymer film material it will normally be necessary

to incorporate in the films for use in the invention a component that enhances non-adherence to protein.

Such components enhancing non-adherence are, for example, poly siloxanes and fluorinated or perfluorinated polymers either individually or in admixture.

A polysiloxane may be present in a polymer film material in the form of a block co-polymer formed with the biodegradable polymer, or added as a block co-polymer formed with another species which facilitates its incorporation into the biodegradable polymer or in any other desired way.

Alternatively, it may be present as a wholly or partially separate surface layer on the biodegradable polymer.

In any case, the presence of a polysiloxane on or in the surface of the biodegradable polymeric films of the invention reduces the incidence of adhesion formation in animal models. The risk of adhesion formation tends to reduce as the surface concentration of polysiloxane increases. Too high a level of polysiloxane, however, reduces the mechanical strength of the film to an unacceptable degree. For the purposes of the invention the film must have sufficient tear strength to allow it to be handled by the surgeon without tearing and to be sutured securely in place. Moreover, once it is in place it must withstand the stresses imposed, particularly on the suture sites, caused by normal bodily function.

Generally the polysiloxane will be present in the film of the invention in an amount of 1 to 20% mole percent and normally in an amount between 1 and 10% mole percent.

The polysiloxane component of the film may, for example, comprise polydimethylsiloxane or a co-polymer thereof and when incorporated to a polyesterurethane is preferably a hydroxy terminated polysiloxane.

The biodegradable polymer may be any polymeric material, including filled polymers, composites, laminates and co-polymers, having a glass transition temperature below about human body temperature (say 40°c) and being either non-crystalline or having a degree or form of crystallinity that allows the film to remain soft and flexible in vivo. Hard, stiff or rigid films or films that become hard, stiff or rigid after implantation tend to give a relatively high incidence of adhesion formation. The softness and flexibility such as to allow the film to drape around a 1 cm radius rod also allow it to drape and conform to a surface of an organ around or over which it is placed.

It is also essential in the film of the invention that the degradation products produced by biodegradation should be eliminated from the body and not retained in any organ or tissue for a period of time long in comparison with the time required for the film itself to degrade. The film and its degradation products must, of course, be biocompatible, non-toxic, non-mutagenic and non-plastogenic (non-genotoxic).

The period over which the film biodegrades in vivo is preferably between 7 and 28 days. The time for biodegradation depends on the chemical constitution of the film and its thickness as well as the biological enviroment in which it is used.

The biodegradable polymer is preferably a polyester polyurethane in which the polyester is an aliphatic fatty acid polyester glycol preferably selected from polycaprolactone diol (preferably of molecular weight between 500 and 2500), poly(ethylene adipate) glycol, poly(tetramethylene adipate) glycol and poly(hexamethylene adipate) glycol (preferably of molecular weight of the order of 2000), or a combination of any of these glycols. These glycols differ systematically in their rates of biodegradation, according to the concentration of ester groups in their structure, and by judicious selection of the polyester glycol or of combinations of

polyester glycols the rate of degradation, in vivo, may be controlled to a considerable extent.

The diisocyanate component of the polyether polyurethane is preferably 4,4 - diphenyl methane diisocyanate or 4,4'-dicyclohexyl methane diiosocyanates although other isocyanates are usable.

A chain extender is prferably also incorporated in the polyester polyurethane. ßutane diol is the preferred material in order to minimise the risk of forming toxic degradation products.

Polyester polyurethane/polysiloxane block co-polymers for use in the invention are preferably prepared using hydroxy ethylether terminated polysiloxanes prepared by reacting a silanol terminated polysiloxane with ethylene oxide or hydroxyl allyl terminated polysiloxanes prepared by reacting allylic alcohol with a hydride terminated polysiloxane.

The polyester polyurethane/siloxane co-polymers may be prepared by any desired method, for example by first mixing the aliphatic polyester with the polysiloxane in the desired ratio, then adding the diioscyanate in excess and finally adding the chain extender, for example, butane diol.

The ratio of polyester glycol to chain extender is preferably of the order of 1:1. The diisocyanate is preferably used in substantially stoichiometric amount to react with the polyester and chain extender.

Examples of polyester/polyurethane/polysiloxane block co-polymers that have been successfully used in the prevention of adhesion formation are based on 4,4'-diphenyl methane diisocyanate, polytetramethylene adipate glycol and 2.5 mol % polydimethylsiloxane: 4,4' diphenyl methane diiosocyanate/polyethylene adipate glycol and 2.5 mol % polydimethlysiloxane and 4-4'dicyclohexylmethane

diiosocyanate/polytetramethylene adipate glycol with 2.5 mol % polydimethylsiloxane. In these polymers the mol percentage of polysiloxane is based on the polyester rather than on the polyester polyurethane.

An alternative biodegradable polymeric material suitable for use in the invention is a lactide polymer of which the glass transition temperature has been reduced by co-polymerisation to below about 40°c so as to provide a soft flexible material suitable for film formation and which is such that the crystallinity does not render the film stiff in vivo, for example, by use of a racemic mixture of the d- and l- forms of polylactic acid.

Films for use in the invention may be cast from solution or extruded from the melt or produced by any other known method. Suitable film thicknesses are within the range of 10 to 60 microns since films of such thickness have adequate tear strength and drape properties. The preferred thickness will depend upon on the intrinsic stiffness or elastic modulus of the material from which the film is made.

If desired, in some cases it is possible to formulate the film forming material in a form in which it can be sprayed or painted over the traumatized tissue area to form, in situ, a substantially continuous film or layer over the said tissue area.

In use the films of the invention will normally be sutured in position but it is possible to use a film that carries on one surface a layer of a non-toxic biodegradable adhesive that allows that side to be adhered over the traumatized region of tissue while the other, outwardly disposed, surface is a surface which is non-adherent to protein. Suitable adhesives for this purpose may be based upon polyacrylic acid or proteins such as fibrin.

The following examples illustrate the invention.

Example 1

A series of polyester polyurethane-polydimethylsiloxane co-polymers were prepared using the following basic technique:
The polyester glycol ($10^{-2}$ mol) was placed in multinecked reaction flask equipped with stirrer condenser guarded with a calcium chloride drying tube, gas bubbler, thermometer and dropping funnel. Dimethylsulfoxide was added via the dropping funnel and the mixture was stirred at a temperature of 60°C until all the polyester had dissolved.

The desired amount of polydimethylsiloxane dissolved in dimethylsulfoxide was added to the reaction flask with rapid stirring at 60°C and stirring was continued out at that temperature for 30 minutes to obtain uniform mixing of the polydimethylsiloxane and the polyester glycol.

The polydimethylsiloxane used was an A-B-A block co-polymer of ethylene oxide and dimethylsiloxane of the general formula $HO-(CH_2)_2-O-(CH_2)_a-[Si(CH_3)_2-O]_y(CH_2)_a-O-(CH_2)_2-OH$ of molecular weight 2064.

The diiosocyanate dissolved in N, N-dimethylformamide in a 5 to 10% excess of a $2 \times 10^{-2}$ mol amount was added dropwise to the reaction flask through the dropping funnel with rapid stirring at 60°C and stirring was continued at that temperature for one hour.

Butane diol in the stoichiometric amount required to react with the residual diiosocyanate dissolved in N, N- dimethylformamide was then added dropwise through the dropping funnel with rapid stirring at 60°C.

The temperature was gradually raised to 125 to 135°C and the mixture was stirred for five hours at that temperature. The

resulting solution which was highly viscous and slightly cloudy was cooled to room temperature under nitrogen and the polymer was isolated by precipitation in methanol. The polymer was reprecipitated twice from tetrahydrofuran to remove impurities and was dried under vacuum at room temperature over silica gel for seven days.

The range of polyester polyurethane/polydimethylsiloxane co-polymers produced is shown in the following Table 1.

## TABLE NO. 1.
## POLYURETHANES SYNTHESIZED (Molar proportions of reactants)

MDI = 4, 4' - Diphenylmethane diisocyanate

$H_{12}MDI$ = 4, 4' - Dicyclohexylmethane diisocyanate

(AR = Aromatic)
(AL = Aliphatic)

BD = Butane diol.

PCL = Polycaprolactone diol,
(H = High molecular weight = 2436)
(M = Intermediate molecular weight = 1250)
(L = Low molecular weight = 540)

PEAG = Poly (ethylene adipate) glycol, Molecular weight = 2010

PTAG = Poly (tetramethylene adipate) glycol, Molecular weight = 2206

PHAG = Poly (hexamethylene adipate) glycol, Molecular weight = 2003

PDMS = Polydimethylsiloxane, Molecular weight = 2064

( % number refers to mole % of PDMS relative to polyester )

POLYURETHANES SYNTHESIZED (Molar proportions of reactants)

| NO. | CODE | MDI (Aromatic) | $H_{12}$MDI (Aliphatic) | BD | PCL | PEAG | PTAG | PHAG | PDMS |
|---|---|---|---|---|---|---|---|---|---|
| -- | MDI/PCL materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 1 | AR / PCL(L) / 0% | 2.06 | ------ | 1.060 | 1.00 | ------ | ------ | ------ | ------ |
| 2 | AR / PCL(M) / 10% | 2.26 | ------ | 1.160 | 1.00 | ------ | ------ | ------ | 0.100 |
| 3 | AR / PCL(M) / 5% | 2.16 | ------ | 1.110 | 1.00 | ------ | ------ | ------ | 0.050 |
| 4 | AR / PCL(M) / 2.5% | 2.11 | ------ | 1.085 | 1.00 | ------ | ------ | ------ | 0.025 |
| 5 | AR / PCL(M) / 0% | 2.06 | ------ | 1.060 | 1.00 | ------ | ------ | ------ | ------ |
| 6 | AR / PCL(H) / 100% | 3.06 | ------ | 1.060 | 1.00 | ------ | ------ | ------ | 1.000 |
| 7 | AR / PCL(H) / 100% | 4.06 | ------ | 2.060 | 1.00 | ------ | ------ | ------ | 1.000 |
| 8 | AR / PCL(H) / 50% | 3.06 | ------ | 1.560 | 1.00 | ------ | ------ | ------ | 0.500 |
| 9 | AR / PCL(H) / 10% | 2.26 | ------ | 1.160 | 1.00 | ------ | ------ | ------ | 0.100 |
| 10 | AR / PCL(H) / 7.5% | 2.21 | ------ | 1.135 | 1.00 | ------ | ------ | ------ | 0.075 |
| 11 | AR / PCL(H) / 5% | 2.16 | ------ | 1.110 | 1.00 | ------ | ------ | ------ | 0.050 |
| 12 | AR / PCL(H) / 2.5% | 2.11 | ------ | 1.085 | 1.00 | ------ | ------ | ------ | 0.025 |
| 13 | AR / PCL(H) / 0% | 2.06 | ------ | 1.060 | 1.00 | ------ | ------ | ------ | ------ |

Continiued.....

TABLE OF POLYURETHANES SYNTHESIZED (Molar proportions of reactants)

| NO. | CODE | MDI (Aromatic) | $H_{12}$MDI (Aliphatic) | BD | PCL | PEAG | PTAG | PHAG | PDMS |
|---|---|---|---|---|---|---|---|---|---|
| -- | MDI/PEAG materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 14 | AR / PEAG / 10% | 2.26 | ------ | 1.160 | ------ | 1.00 | ------ | ------ | 0.100 |
| 15 | AR / PEAG / 7.5% | 2.21 | ------ | 1.135 | ------ | 1.00 | ------ | ------ | 0.075 |
| 16 | AR / PEAG / 5% | 2.16 | ------ | 1.110 | ------ | 1.00 | ------ | ------ | 0.050 |
| 17 | AR / PEAG / 2.5% | 2.11 | ------ | 1.085 | ------ | 1.00 | ------ | ------ | 0.025 |
| 18 | AR / PEAG / 0% | 2.06 | ------ | 1.060 | ------ | 1.00 | ------ | ------ | ------ |
| -- | MDI/PTAG materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 19 | AR / PTAG / 10% | 2.26 | ------ | 1.160 | ------ | ------ | 1.00 | ------ | 0.100 |
| 20 | AR / PTAG / 7.5% | 2.21 | ------ | 1.135 | ------ | ------ | 1.00 | ------ | 0.075 |
| 21 | AR / PTAG / 5% | 2.16 | ------ | 1.110 | ------ | ------ | 1.00 | ------ | 0.050 |
| 22 | AR / PTAG / 2.5% | 2.11 | ------ | 1.085 | ------ | ------ | 1.00 | ------ | 0.025 |
| 23 | AR / PTAG / 0% | 2.06 | ------ | 1.060 | ------ | ------ | 1.00 | ------ | ------ |

Continued.....

TABLE OF POLYURETHANES SYNTHESIZED (Molar proportions of reactants)

| NO. | CODE | MDI (Aromatic) | $H_{12}$MDI (Aliphatic) | BD | PCL | PEAG | PTAG | PHAG | PDMS |
|---|---|---|---|---|---|---|---|---|---|
| -- | MDI/PHAG materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 24 | AR / PHAG / 10% | 2.26 | ------ | 1.160 | ------ | ------ | ------ | 1.00 | 0.100 |
| 25 | AR / PHAG / 7.5% | 2.21 | ------ | 1.135 | ------ | ------ | ------ | 1.00 | 0.075 |
| 26 | AR / PHAG / 5% | 2.16 | ------ | 1.110 | ------ | ------ | ------ | 1.00 | 0.050 |
| 27 | AR / PHAG / 2.5% | 2.11 | ------ | 1.085 | ------ | ------ | ------ | 1.00 | 0.025 |
| 28 | AR / PHAG / 0% | 2.06 | ------ | 1.060 | ------ | ------ | ------ | 1.00 | ------ |
| -- | $H_{12}$MDI materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 29 | AL / PEAG / 2.5% | ------ | 2.11 | 1.085 | ------ | 1.00 | ------ | ------ | 0.025 |
| 30 | AL / PTAG / 2.5% | ------ | 2.11 | 1.085 | ------ | ------ | 1.00 | ------ | 0.025 |

The various polyesterurethanes/polysiloxane copolymers produced were tested for adherence to protein by the gelatin adhesion test carried out as follows:

Films of the various copolymers were prepared from a 7% solution in tetrahydrofuran by casting the solution onto cleaned glass slides using a micropipette. Evaporation of the solvent was controlled by covering the slides with glass Petri dishes. After 24 hours the films were peeled from the glass slides and dried under vacuum at room temperature for a further 72 hours.

The polymer films were placed on a flat surface with either the air contact side or the glass contact side upwards. A PTFE window frame mould was placed on top of the film and filled with a warm gelatin solution produced by dissolving 40 grammes of gelatin in 100 mils of water at a temperature of 60°C. The gelatin used was leaf gelatin derived from pig skin having a pH of 5.0 to 5.5. The film casting temperature was between 58 and 60°C. When the gelatin had set the specimens were transferred to an oven pre-set at 37°C and the gelatin was dried at this temperature for 48 hours.

After drying the specimens were removed from the moulds leaving a gelatin slab sticking to the surface of the film and this was subsequently peeled off using a 180° degree peel angle on a JJ table model testing machine at a cross head speed of 100mm per minute.

The results are shown in Table 2.

Also shown in Table 2 are the results of in vivo adhesion testing and degradation for certain of the polyester polyurethanes.

TABLE 2

RESULTS OF IN-VITRO & IN-VIVO STUDIES

| NO. | CODE | THICKNESS (microns) | 4% MODULUS (MPa) | ALKALINE HYDROLYSIS (Half life)* (DAYS) | IN-VITRO ADHESIONS J/m$^2$ | | IN-VIVO ADHESIONS | |
|---|---|---|---|---|---|---|---|---|
| | | | | | AIR | GLASS | %Adhesion | % Film loss |
| (1) | MDI/PCL materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 1 | AR / PCL(L) / 0.00% | 40 - 60 | 20 | ..... | ..... | ..... | ..... | ..... |
| 2 | AR / PCL(M) / 10.00% | 40 - 60 | 41 | 5 | 0 | 101 | ..... | ..... |
| 3 | AR / PCL(M) / 5.00% | 40 - 60 | 43 | ..... | 5 | 121 | ..... | ..... |
| 4 | AR / PCL(M) / 2.50% | 40 - 60 | 67 | 20 | 13 | 215 | ..... | ..... |
| 5 | AR / PCL(M) / 0.00% | 40 - 60 | 58 | 22 | 1376 | Tear in film | ..... | ..... |
| 6 | AR / PCL(H) / 100.00% | ..... | ..... | ..... | ..... | ..... | ..... | ..... |
| 7 | AR / PCL(H) / 100.00% | ..... | ..... | ..... | ..... | ..... | ..... | ..... |
| 8 | AR / PCL(H) / 50.00% | ..... | ..... | ..... | ..... | ..... | ..... | ..... |
| 9 | AR / PCL(H) / 10.00% | 40 - 60 | 16 | ..... | 0 | 84 | ..... | ..... |
| 10 | AR / PCL(H) / 7.50% | 40 - 60 | 13 | ..... | 0 | 93 | ..... | ..... |
| 11 | AR / PCL(H) / 5.00% | 40 - 60 | 11 | ..... | 3 | 132 | ..... | ..... |
| 12 | AR / PCL(H) / 2.50% | 40 - 60 | 19 | ..... | 10 | 246 | ..... | ..... |
| 13 | AR / PCL(H) / 0.00% | 40 - 60 | 18 | ..... | Tear in film | Tear in film | ..... | ..... |

Continued.....

* Half-life based on extensibility

RESULTS OF IN-VITRO & IN-VIVO STUDIES

| NO. | CODE | THICKNESS (microns) | 4% MODULUS (MPa) | ALKALINE HYDROLYSIS (Half life)* (DAYS) | IN-VITRO ADHESIONS J/m² | | IN-VIVO ADHESIONS | |
|---|---|---|---|---|---|---|---|---|
| | | | | | AIR | GLASS | %Adhesion | % Film loss |
| (2) | MDI/PEAG materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 14 | AR / PEAG / 10.00% | 40 - 60 | 227 | ..... | 0 | 87 | ..... | ..... |
| 15 | AR / PEAG / 7.50% | 40 - 60 | 245 | ..... | 0 | 100 | ..... | ..... |
| 16 | AR / PEAG / 5.00% | 40 - 60 | 265 | ..... | 4 | 142 | ..... | ..... |
| 17 | AR / PEAG / 2.50% | 40 - 60 | 297 | ..... | 5 | 210 | ..... | ..... |
| 17A | AR / PEAG / 2.50% | 30 - 40 | ..... | ..... | 2 | 108 | 12 | 100 |
| 18 | AR / PEAG / 0.00% | 40 - 60 | 263 | ..... | 1498 | Tear in film | ..... | ..... |
| (3) | MDI/PTAG materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 19 | AR / PTAG / 10.00% | 40 - 60 | 460 | 27 | 0 | 45 | ..... | ..... |
| 20 | AR / PTAG / 7.50% | 40 - 60 | 410 | ..... | 0 | 71 | ..... | ..... |
| 21 | AR / PTAG / 5.00% | 40 - 60 | 395 | ..... | 0 | 112 | ..... | ..... |
| 22 | AR / PTAG / 2.50% | 40 - 50 | 368 | 26 | 1 | 119 | 11 | 50 |
| 22A | AR / PTAG / 2.50% | 20 - 30 | ..... | ..... | 0 | 96 | 9 | 50 |
| 23 | AR / PTAG / 0.00% | 40 - 60 | 389 | 22 | 1066 | 1240 | ..... | ..... |

Continued.....

* Half-life based on extensibility

RESULTS OF IN-VITRO & IN-VIVO STUDIES

| NO. | CODE | THICKNESS (microns) | 4% MODULUS (MPa) | ALKALINE HYDROLYSIS (Half life)* (DAYS) | IN-VITRO ADHESIONS J/m² | | IN-VIVO ADHESIONS | |
|---|---|---|---|---|---|---|---|---|
| | | | | | AIR | GLASS | %Adhesion | % Film loss |
| (4) | MDI/PHAG materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 24 | AR / PHAG / 10.00% | 40 - 60 | 528 | 27 | 0 | 127 | ..... | ..... |
| 25 | AR / PHAG / 7.50% | 40 - 60 | 532 | ..... | 0 | 209 | ..... | ..... |
| 26 | AR / PHAG / 5.00% | 40 - 60 | 435 | ..... | 0 | 217 | ..... | ..... |
| 27 | AR / PHAG / 2.50% | 40 - 60 | 478 | 30 | 3 | 253 | ..... | ..... |
| 28 | AR / PHAG / 0.00% | 40 - 60 | 475 | 30 | Tear in film | Tear in film | ..... | ..... |
| (5) | $H_{12}$MDI materials | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 29 | AL / PEAG / 2.50% | 40 - 60 | ..... | ..... | 3 | 96 | ..... | ..... |
| 30 | AL / PTAG / 2.50% | 40 - 60 | 208 | ..... | ..... | ..... | ..... | ..... |
| 30A | AL / PTAG / 2.50% | 30 -40 | ..... | ..... | 2 | ≈ 92 | 67 | 50 |
| 30B | AL / PTAG / 2.50% | 20 -30 | ..... | ..... | 2 | 85 | 27 | 50 |

* Half-life based on extensibility

For the in vivo adhesion testing female Sprague-Dawley rats ranging in weight from 225 to 250 grammes were used. A mid line laparotomy was carried under anaesthetic and the caecum was delivered out of the wound onto a moist swab. The anterior surface adjacent the ante-mesenteric border of the caecum was then scraped with a No.15 scalpel blade until the serosal layer was damaged over an area 1.5 x 1cm.

The test films were sterilised prior to implantation by soaking the film in 70% absolute alcohol for 2 hours. The film was cut to side 1.5 x 1cm and placed non-adherent size upwards on the injury site and anchored in place with six sutures, four at the corners and two along the middle of the longest edge.

The caecum was them returned to the adominal cavity and the wound closed. For control animals six sutures were stitched around the wound area, four at the corners and two at the middle of the long side.

Adhesions were graded on a scale from 0 to IV, grade 0 indicating no adhesion and I, II, III and IV being low, moderate, high and maximum adhesions respective.

The results were as follows:

1. AR/PEAG/2.5% (20-30 micron)

Studies were performed on 22 rats, 12 received implants and 10 were control at 2 weeks only 1 animal out of 6 of the implanted rat had grade I adhesions. The film was completely dissolved and only the sutures could be seen. At 4 weeks, of 6 animals 1 had grade I and 1 had grade III adhesions. The grade III adhesions were found on the sutures. The film was completely degraded.

In the control animals grade III or grade IV adhesions were present in all the rats.

2. AR/PTAG/2.5% (40 to 50 micron)

25 rats were operated upon of which 13 received implants and 12 were controls. Autopsy was carried out at 2 and 4 week. 7 of the implant group and 6 controls were killed at 2 weeks and the remaining 6 animals remaining from each group were killed at 4 weeks.

One grade II and one grade III adhesion were found in 2 of the 13 implanted rats. There were no adhesions in the other 11. Grade III or grade IV adhesions were found in all of the controls. Degradation of the film was noticable at 4 weeks but the film was still intact.

3. AR/PTAG/2.5% (20 to 30 micron)

25 rats were used of which 13 received implants and 12 were controls.

In the implant group, after 2 weeks 1 animal out of 7 had grade II adhesions and at 4 weeks two animals had grade I adhesions. Grade III and grade IV adhesions were present in all the 12 control animals. At four weeks the film was partially degraded.

4. AL/PTAG/2.5% (40 - 50 micron)

12 rats, 7 implanted and 5 control, were operated on. At four weeks the implanted rats had grade II or grade III adhesions while the control animals all had grade III or grade IV adhesions.

5. AL/PTAG/2.5% (20 to 30 microns)

12 rats, 7 implanted and 5 controlled were operated on.

At 2 weeks six of the implanted animals had grade I adhesions and

the remaining animal had no adhesions. Adhesions present were all at the suture sites and/or the edge of the film. The film was partially degraded and was slightly stiffer.

In the control animals grade III adhesions were found in four animals and one animal had grade IV adhesions.

C L A I M S :

1. A substantially continuous film for use as a barrier for the prevention of post-surgical adhesions, which film (1) is formed predominately from a physiologically tolerable polymer or mixture of polymers that it is substantially completely biodegradable in vivo, (2) consists predominately of polymer having a glass transition temperature lower than 40°C; (3) it has at least one surface which is non-adherent (as herein defined) to protein, (4) has drape properties such that at 40°C it can be wrapped around a one centimetre radius rod without exhibiting spring-back tendency; and (5) has a tear strength such as to allow it to be sutured into place in the human body and remain in position until advanced biodegradation has occurred.

2. A film according to Claim 1, wherein non-adherence to protein is achieved by incorporation in the film of low-surface-energy polymers or copolymers containing polysiloxanes and/or fluorinated side-groups.

3. A film according to Claim 1 or Claim 2, wherein the low-surface-energy polymer or copolymer is present as a block copolymer formed with the biodegradable polymer or added as a block copolymer formed with another species that facilitates its incorporation into the biodegradable polymer.

4. A film according to Claim 1 or Claim 2, wherein the low surface energy polymer or copolymer is present as a wholly or partially separate surface layer on the biodegradable polymer.

5. A film according to any one of Claims 1 to 4, wherein the biodegradable polymer is a polyester polyurethane.

6. A film according to Claim 5, wherein the polyester component of the polyester polyurethane is an aliphatic polyester.

7. A film according to Claim 6, wherein the polyester is polycaprolactone diol, poly(ethylene adipate) glycol, poly(tetramethylene adiphate) glycol or poly(hexamethylene adipate) glycol.

8. A film according to any of Claims 5 to 7, where the polyester polyurethane is formed from at least two different polyesters.

9. A film according to any one of Claims 2 to 8, wherein the low surface energy polymer or copolymer is present in the film in a concentration of less than 20 mole %.

10. A film according to Claim 9, wherein the low surface energy polymer or copolymer is present in the film at a concentration between 1.0 and 10.0 mole %.

11. A film according to Claim 1, produced from a polyester polyurethan/polysiloxane block copolymer of which the polyester polyurethan is produced from 4,4'-diphenylmethane diisocyanate or 4,4' dicyclohexylmethane diisocyanate and a mixture of poly(ethylene adipate) glycol or poly(tetra ethylene)adipate glycol and butane diol and 2.5 mol % of a polydimethylsiloxane, based on the polyester.

12. A film according to any one of Claims 1 to 11, which is from 10 to 60 microns thick.

13. A film according to any one of Claims 1 to 12, bearing on one side a physiologically tolerable adhesive such as to allow it to be adhered at least temporarily to wet living tissue.

14. A film according to any one of Claims 1 to 13, which can be deposited from solution by spraying or painting onto a tissue surface to be protected.

# INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 93/02186

A. CLASSIFICATION F SUBJECT MATTER
IPC 5 A61L31/00 C08G77/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61L C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| Y | EP,A,0 213 563 (JOHNSON & JOHNSON PRODUCTS INC.) 11 March 1987<br>see claims | 1-6,9, 10,12 |
| A | EP,A,0 089 780 (WARNER-LAMBERT COMPANY) 28 September 1983<br>see claims; examples<br>see page 17, line 25 - line 30 | 6-12 |
| A | WO,A,90 00067 (ASTRA MEDITEC AKTIEBOLAGET) 11 January 1990 | |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 1 February 1994 | 09. 02. 94 |

| Name and mailing address of the ISA | Authorized officer |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | Cousins-Van Steen, G |

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